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Amiodarone: Risk Factors for Recurrence of Symptomatic Ventricular Tachycardia Identified at Electrophysiologic Study

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Ventricular tachycardia induced by programmed electrical stimulation during amiodarone therapy often does not preclude a good clinical response. The purpose of this study was to determine whether use of discriminant analysis could distinguish patients who remained asymptomatic from those who subsequently developed symptomatic ventricular tachycardia or cardiac arrest. Studies were performed in 37 patients with sustained ventricular tachycardia who still had ventricular tachycardia induced during programmed electrical stimulation during amiodarone therapy. The mean follow-up time was 14.1 ± 1.3 months (±SEM). Twenty-three patients remained asymptomatic, whereas 14 patients had symptomatic recurrence of their ventricular tachycardia.

In patients with recurrence of arrhythmia compared with asymptomatic patients, administration of amiodarone caused a longer ventricular effective refractory period (296 ± 8 versus 271 ± 7 ms, $p < 0.05$) and a greater change in corrected QT [QT_c] interval (90 ± 18 versus 44 ± 9 ms, $p < 0.02$), but no difference in the decrease in premature ventricular complexes after treatment with amiodarone. During amiodarone therapy, nonbundle branch reentrant repetitive ventricular responses were induced by a single ventricular extrastimulus during sinus rhythm in 9 of 14 patients with recurrent arrhythmias compared with 2 of 21 asymptomatic patients ($p = 0.001$). Also, less aggressive pacing techniques were required to induce ventricular tachycardia in 9 of 14 symptomatic patients compared with 4 of 23 asymptomatic patients ($p < 0.02$). A discriminant analysis using the presence of nonbundle branch reentrant repetitive ventricular responses, change in method of ventricular tachycardia induction and either the change in QT_c interval or ventricular effective refractory period correctly identified clinical outcome in 90% of the patients, and all patients with recurrent arrhythmias were classified correctly. It is concluded that electrophysiologic testing during amiodarone therapy can provide data that identify patients who appear to be at risk for development of ventricular tachycardia after hospital discharge.

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Serial electrophysiologic testing is a sensitive and specific method for predicting clinical response to some antiarrhythmic drugs in patients with recurrent sustained ventricular tachycardia (1,2). However, we (3) and other investigators (4,5) have reported that many patients may remain asymptomatic during amiodarone therapy despite induction of ventricular tachycardia during serial electrophysiologic testing with this agent. It has therefore been suggested that high risk patients be treated with amiodarone empirically without the aid of invasive testing (6,7). Such a recommendation fails to consider that factors other than the initiation of ventricular tachycardia may be useful to determine the clinical outcome of patients taking amiodarone. The purpose of this study was to investigate the hypothesis that combinations of electrophysiologic variables are useful to identify patients who appear at increased risk for recurrence of symptomatic ventricular tachycardia or sudden death during amiodarone therapy.

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Methods

Study patients. The study group comprised 37 patients, including 28 men and 9 women aged 55 ± 3 years (mean ± SEM). Twenty-six had coronary artery disease demonstrated by a documented myocardial infarction or cineangiographic presence of 75% or greater stenosis of one or more coronary arteries, or both. Entry criteria included recurrence of sustained ventricular tachycardia despite treatment with conventional agents and often two to three investigational antiarrhythmic drugs, induction of ventricular tachycardia during a drug-free control electrophysiologic study and ventricular tachycardia still induced at repeat electrophysiologic study 14 to 21 days after initiation of amiodarone therapy (800 mg/day). Although several months of amiodarone therapy are needed to achieve steady state conditions, it is not feasible to keep patients in the hospital for this length of time before repeating electrophysiologic studies. Thus, electrophysiologic testing was performed after 2 to 3 weeks of amiodarone therapy to investigate the hypothesis that data obtained at this time would identify patients most susceptible to recurrence of arrhythmias. Two additional patients had no ventricular tachycardia induced during amiodarone therapy and were excluded from further analysis.

Study protocol. All patients were admitted to a telemetry unit where their cardiac rhythm was monitored continuously. A 24 hour ambulatory electrocardiographic recording and an exercise test were performed in the control state before electrophysiologic testing if the patient's rhythm was stable, and 24 to 48 hours before the scheduled repeat electrophysiologic study while the patient received amiodarone. If ventricular tachycardia was noted on either test during amiodarone treatment, a second antiarrhythmic agent was added to amiodarone and the noninvasive tests were repeated. Seventeen patients received amiodarone and another antiarrhythmic agent. These drugs included encainide (n = 5), aprindine (n = 5), mexiletine (n = 2), disopyramide (n = 2), procainamide (n = 2) and quinidine (n = 1).

Electrophysiologic testing during amiodarone therapy was performed when no ventricular tachycardia was demonstrated on noninvasive testing. Thirty-five patients had a repeat 24 hour electrocardiographic recording performed before electrophysiologic drug study. Of these 35 patients, 18 were receiving therapy with amiodarone alone and 17 were taking amiodarone in addition to a second antiarrhythmic agent. Two patients taking amiodarone alone did not have a 24 hour electrocardiographic recording before repeat electrophysiologic study.

Long-term electrocardiographic recording. A continuous 24 hour ambulatory electrocardiographic recording was performed in 35 of 37 patients before the final electrophysiologic drug study. In 16 of these 35 patients a continuous electrocardiographic recording was performed before and after 12 to 15 days of single drug therapy with amiodarone. In all patients a 24 hour printout of the electrocardiogram (7700 Eliminator, American Edwards Laboratories) was obtained and the number of premature ventricular complexes was counted manually by the authors. Sections of each record were printed out at 25 mm/s paper speed to verify the ventricular origin of the wide QRS complexes.

Pacing protocol. The pacing protocol to induce ventricular tachycardia has been reported previously in detail (2). Briefly, single and double premature ventricular stimuli were induced during sinus rhythm and at ventricular pacing cycle lengths of 600, 500 and 400 ms, scanning diastole to the point of ventricular refractoriness. Burst right ventricular pacing of three to eight complexes at cycle lengths of 250 ms or more was also performed. If ventricular tachycardia was not induced at the right ventricular apex, the stimulation protocol was repeated at the right ventricular outflow tract. An arbitrary hierachy of pacing techniques (Fig. 1) was defined to determine whether a more or less aggressive pacing technique was needed to induce ventricular tachycardia during amiodarone therapy. In general, a complete pacing protocol was performed at both ventricular sites unless sustained ventricular tachycardia was reproducibly induced before completion of the protocol.

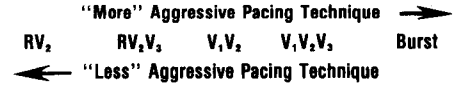
Long-term amiodarone dosage. All patients were discharged receiving 800 mg/day of amiodarone. This dosage was decreased to 600 mg/day after 1 to 4 months of treatment, and then to 400 mg/day after 4 to 8 months. Plasma levels of amiodarone were not available during this study.

Follow-up. Patients were followed up in the arrhythmia clinic and seen 1 month after discharge and every 3 months thereafter. They were questioned in detail about potential drug side effects and recurrence of symptoms. Outpatient 24 hour continuous electrocardiographic recordings were performed routinely 6 months after discharge, or if warranted by symptoms suggestive of recurrent arrhythmia.

Definitions. *Nonbundle branch reentrant repetitive ventricular response (8)* is defined as a second ventricular complex not due to bundle branch reentry that follows an induced premature ventricular complex initiated during sinus rhythm.

Inducible ventricular tachycardia (8) is defined as three or more consecutive nonbundle branch reentrant repetitive ventricular responses.

Figure 1. Hierarchy of ventricular stimulation techniques used to initiate ventricular tachycardia. Burst = 3 to 8 ventricular complexes at cycle lengths of 250 ms or more; RV_2 = 1 ventricular extrastimulus introduced during sinus rhythm; RV_2V_3 = 2 ventricular extrastimuli introduced during sinus rhythm; V_1V_2 = 1 ventricular extrastimulus introduced during ventricular pacing; $V_1V_2V_3$ = 2 ventricular extrastimuli introduced during ventricular pacing.



Sustained ventricular tachycardia (2) is defined as ventricular tachycardia lasting 30 seconds or more or requiring termination before 30 seconds because of hemodynamic compromise.

Nonsustained ventricular tachycardia (2) is defined as ventricular tachycardia of three beats to less than 30 seconds in duration.

Statistical analysis. Comparisons between symptomatic and asymptomatic patients were made using *t* tests for continuous variables. Categorical variables were analyzed using the chi-square test for contingency tables. Fisher's exact test was used for 2 × 2 tables (9). Multivariate analysis to determine the set of variables that best predicted outcome was performed using stepwise discriminant analysis and the Cox proportional hazards linear model (10,11). The Mann-Whitney U test was used to analyze premature ventricular complex counts before and during drug therapy because the counts do not have a Gaussian distribution.

Results

Patient characteristics (Table 1). Twenty-three treated patients (asymptomatic group) had neither recurrence of symptoms suggestive of ventricular tachycardia nor any ventricular tachycardia recorded during outpatient 24 hour ambulatory continuous electrocardiographic recordings performed every 3 to 6 months. Fourteen treated patients (symptomatic group) had symptomatic events after hospital discharge; sustained ventricular tachycardia occurred in 11 and sudden death in 3 patients (Fig. 2). There was no statistical difference between symptomatic and asymptomatic patients in age, sex, history of cardiac arrest, presence of coronary artery disease, presence of left ventricular aneurysm or an abnormal (<50%) ejection fraction (Table 1). Similarly, there was no difference between groups in either the number of patients who received an antiarrhythmic agent in addition to amiodarone or in the mean amiodarone dosage at follow-up.

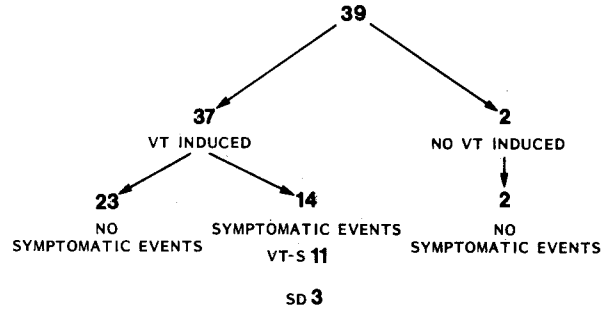


Figure 2. Follow-up data on 39 patients receiving amiodarone therapy for ventricular tachycardia (VT). SD = sudden death; VT-S = sustained ventricular tachycardia.

Comparison of multiple electrophysiologic variables—control study (Table 2). Before drug treatment there was no statistically significant difference between symptomatic and asymptomatic patients in spontaneous sinus cycle length, HV interval, corrected QT interval (12) or ventricular effective and functional refractory periods. The mean cycle length of the inducible ventricular tachycardia was longer in the symptomatic group ($p = 0.03$), as was the value for the ventricular tachycardia cycle length minus the ventricular effective refractory period ($p = 0.04$).

Comparison of multiple electrophysiologic variables—amiodarone study (Table 3). During the electrophysiologic study while the patients received amiodarone there was no statistically significant difference between symptomatic and asymptomatic groups in the spontaneous sinus cycle length, HV interval, corrected QT interval or the value for ventricular tachycardia cycle length minus the ventricular effective refractory period. Both the ventricular effective refractory period ($p = 0.04$) and the mean ventricular tachycardia cycle length were no longer in the symptomatic group. Nonbundle branch reentrant repetitive ventricular response (8) was induced during sinus rhythm with

Table 1. Patient Characteristics (mean ± SEM)

	Asymptomatic (n = 23)	Symptomatic (n = 14)	p Value
Age (yr)	53 ± 3	57 ± 3	NS
Sex			NS
Men	16	12	
Women	7	2	
Etiologic diagnosis			NS
CAD	15	11	
Non-CAD	8	3	
Ejection fraction			NS
Normal	6	1	
Abnormal	17	13	
LV aneurysm	12	10	NS
History of cardiac arrest	15	13	NS

CAD = coronary artery disease; LV = left ventricular; NS = not significant; p = probability value; SEM = standard error of the mean.

Table 2. Electrophysiologic Variables: Control Study (mean ± SEM)

Variable (ms)	Asymptomatic (n = 23)	Symptomatic (n = 14)	p Value
SCL	790 ± 33	813 ± 48	NS
HV	52 ± 3	55 ± 3	NS
QT_c	421 ± 8	406 ± 16	NS
VERP	242 ± 5	255 ± 6	NS
VFRP	270 ± 7	282 ± 6	NS
VT CL	276 ± 18	337 ± 19	0.03
VT CL − VERP	25 ± 14	77 ± 20	0.04

CL = cycle length; HV = HV interval; QT_c = corrected QT_c interval; SCL = spontaneous sinus cycle length; VERP = ventricular effective refractory period; VFRP = ventricular functional refractory period; VT = ventricular tachycardia; other abbreviations as in Table 1.

Table 3. Electrophysiologic Variables: Amiodarone Study (mean ± SEM)

Variable (ms)	Asymptomatic (n = 23)	Symptomatic (n = 14)	p Value
SCL	866 ± 34	888 ± 33	NS
HV	62 ± 3	70 ± 3	NS
QT_c	464 ± 10	499 ± 21	NS
VERP	271 ± 7	296 ± 8	0.04
VFRP	302 ± 9	333 ± 11	0.06
VT CL	354 ± 20	420 ± 25	0.05
VT CL − VERP	69 ± 15	114 ± 22	NS
RVR +	2/21	9/14	0.001

RVR + = positive repetitive ventricular response; other abbreviations as in Tables 1 and 2.

a single ventricular extrastimulus more frequently in the symptomatic than in the asymptomatic group (p = 0.001).

Change in electrophysiologic variables during therapy (Table 4). In comparing the control study with the study in which the patient received amiodarone, there was no significant difference between the symptomatic and asymptomatic groups in the change in sinus cycle length, HV interval, ventricular effective refractory period or ventricular tachycardia cycle length. However, the change in the QT_c interval was greater in the symptomatic than in the asymptomatic group (p = 0.02). In addition, four patients in the group with recurrent ventricular tachycardia developed new nonbundle branch reentrant repetitive ventricular response in contrast to no patient in the asymptomatic group. During the control and amiodarone studies, there was no difference between the asymptomatic and symptomatic groups in the duration of ventricular tachycardia induced by programmed ventricular stimulation.

Method of ventricular tachycardia induction (Fig. 3). Although there was no difference between the asymptomatic and symptomatic groups in the method of induction of ventricular tachycardia during the control study, a difference between groups (p = 0.014) was evident during testing after amiodarone (Fig. 3). Less aggressive pacing techniques were capable of inducing ventricular tachycardia in 9 of 14 patients in the symptomatic group, compared with only 4 of 23 asymptomatic patients. Of particular note is that ventricular tachycardia was induced with one or two extrastimuli introduced during sinus rhythm in six symptomatic patients but in only one asymptomatic patient.

Table 4. Change in Electrophysiologic Variables: Control Study Versus Amiodarone Study (mean ± SEM)

Variable (ms)	Asymptomatic (n = 23)	Symptomatic (n = 14)	p Value
Δ SCL	75 ± 27	65 ± 64	NS
Δ HV	11 ± 3	16 ± 4	NS
Δ QT_c	44 ± 9	90 ± 18	0.02
Δ VERP	29 ± 6	42 ± 12	NS
Δ VFRP	32 ± 8	51 ± 13	NS
Δ VT CL	78 ± 13	83 ± 28	NS
Δ RVR			0.03
Negative to positive	0	4	
Same	18	7	
Positive to negative	3	2	

Abbreviations as in Tables 1, 2 and 3.

Continuous electrocardiographic recording. Thirty-five patients had 24 hour continuous electrocardiographic recordings during drug therapy before hospital discharge. The 24 hour median premature ventricular complex count was 200 (range 0 to 2,591) in the asymptomatic group (n = 22) and 907 (range 0 to 5,346) in the symptomatic group (n = 13) (p = NS). Sixteen patients, eight symptomatic and eight asymptomatic, had a 24 hour continuous electrocardiographic recording before and single drug therapy with amiodarone (Fig. 4). For all patients the 24 hour median premature ventricular complex count was 1,390 (range 13 to 20,790) before therapy and it significantly decreased to 116 (range 0 to 5,346) during amiodarone treatment (p < 0.004). There was no significant difference between symptomatic and asymptomatic patients in premature ventricular complex counts either at control or drug study. Further, amiodarone caused a 90% reduction in premature ventricular complex counts in six of eight asymptomatic patients and four of eight symptomatic patients (p = NS).

Follow-up (Fig. 2). All patients were followed up for a mean of 14.1 ± 1.3 months. Twenty-three patients have remained asymptomatic (mean follow-up time 17.5 ± 1.5 months) and 14 have had symptomatic recurrence of arrhythmia at a mean follow-up time of 8.5 ± 1.6 months. In the symptomatic group, three patients with a prior history of cardiac arrest died suddenly and eight have required cardioversion for recurrence of sustained ventricular tachycardia. Eleven of the 14 arrhythmia recurrences occurred within 4 months of hospital discharge.

Discriminant analysis (Tables 5 and 6). Several variables were significantly different in asymptomatic and symptomatic groups (Tables 2 to 4). However, substantial overlap occurred between groups and no clear break was evident to separate asymptomatic from symptomatic patients. Thus, stepwise discriminant anaylsis was performed to determine which combination of variables led to an increased risk of recurrence. Because variables that are not significantly related to recurrence alone could be significantly related in combination with other variables, all variables previously discussed were included in the analysis.

Discriminant analysis requires that subjects included in the analysis have values for all variables to be considered. Because the change in ventricular effective refractory period after drug therapy appeared to be an important predictor and was only available in 25 patients, two parallel analyses were done. Both involved all other available measurements but only one included change in ventricular effective refractory

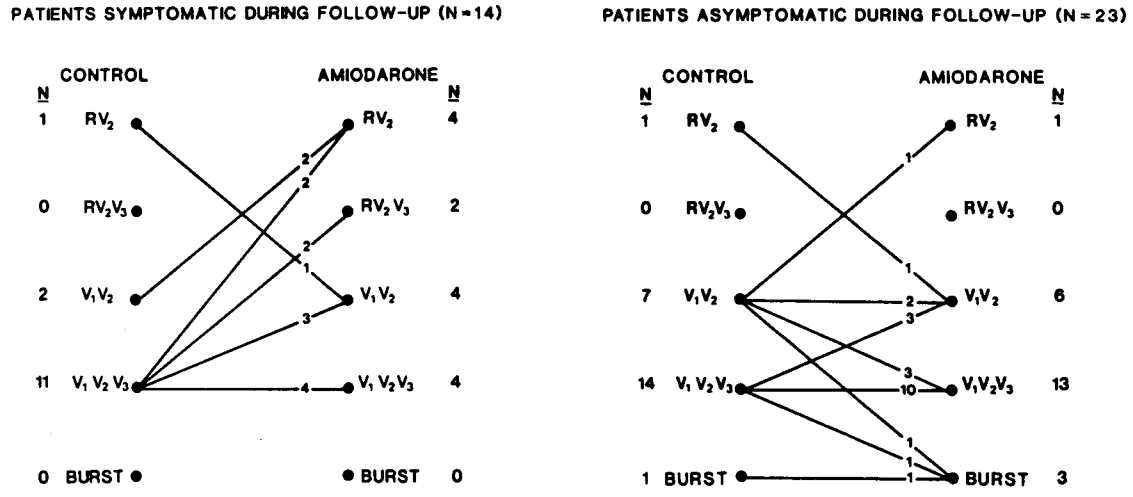


Figure 3. Pacing technique used to initiate ventricular tachycardia in the two patient groups before (control) and during amiodarone therapy. N = number of patients; other abbreviations as in Figure 1.

period. Initial stepwise discriminant analyses included the large set of variables. A final analysis was done with the two best sets of variables to allow inclusion of as many subjects as possible in developing the discriminant functions.

The set of variables leading to increased risk of arrythmia recurrence comprised conversion from negative to positive repetitive ventricular response, increases in QT_c interval or ventricular effective refractory period with drug therapy and easier induction of ventricular tachycardia during drug therapy. A large increase in ventricular effective refractory period in combination with the other two factors was associated with an increased risk of symptomatic recurrence. The significance levels in Tables 5 and 6 indicate the importance of the variable in the discriminant analysis and not its significance in a univariate analysis.

Cox proportional hazards linear model was fitted to determine which combination of all the variables led to increased risk of recurrence under the assumptions of this model. The stepwise Cox regression procedure selected as risk indicators the same three variables—change in QT_c interval or ventricular effective refractory period, change in repetitive ventricular response status and change in method of ventricular tachycardia induction—selected by the discriminant analysis. Again, increases in the QT_c interval or ventricular effective refractory period, change of repetitive ventricular response from negative to positive with drug therapy and easier method of ventricular tachycardia induction with drug therapy were associated with increased risk of recurrence of ventricular tachycardia or cardiac arrest.

Figure 5 displays in a simple format the risk for recurrent events for combinations of the three variables used in the discriminant function. If changes from control to drug study in QT interval or ventricular effective refractory period exceed the values shown, ventricular tachycardia is more likely to recur. The patient with the best chance of remaining asymptomatic during amiodarone therapy would have the values located in the top of the middle column of Figure 5: repetitive ventricular response status changing from positive to negative and ventricular tachycardia during therapy becoming harder to induce, that is, requiring a more aggressive pacing technique. This patient would need a change in QT

Figure 4. Ability of amiodarone therapy to suppress premature ventricular complexes.

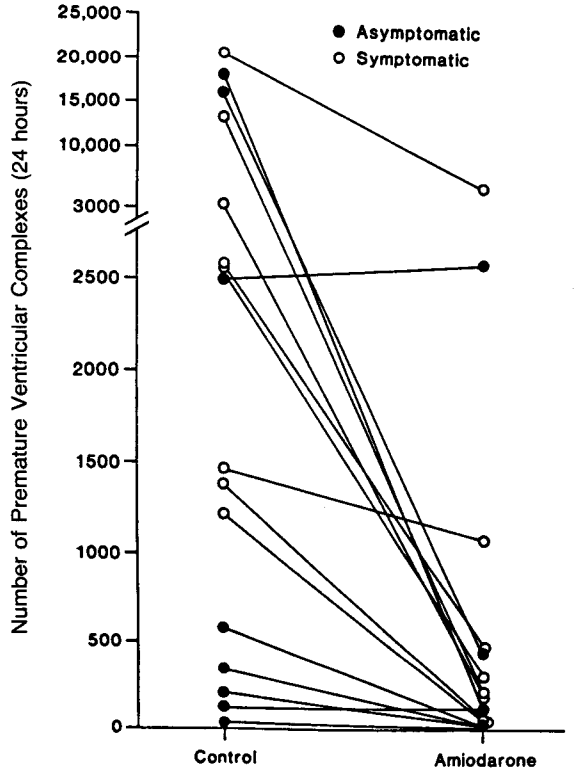


Table 5. Discriminant Analysis (RVR, Δ QT_c and Δ induction method)

Actual Group (n = 31)	Assigned Group: Asymptomatic	Assigned Group: Symptomatic
Asymptomatic 20	17	3
Symptomatic 11	0	11
Classification accuracy = 90.3% (28 of 31)		

Risk Factors	Structure Coefficient*	p Value
Δ QT_c	0.35	<0.001
RVR	0.54	0.003
Δ Ind method	0.49	<0.001
RVR − to + = +1	Ind easier = +1	
RVR same = 0	Ind same = 0	
RVR + to − = −1	Ind harder = −1	

*Structure coefficient gives correlation of variable with discriminant function. A positive value means that larger values of the variable are associated with symptomatic follow-up. Critical value = 0.332 (midpoint of group centroids). Values greater than or equal to critical value predict recurrence; discriminant function = −0.878 + 1.949 (RVR) + 1.130 (Ind) − 0.011 (Δ QT_c). Ind = pacing technique to induce ventricular tachycardia; Δ QT_c = QT_c (drug) − QT_c (control); RVR = repetitive ventricular response.

interval or ventricular effective refractory period greater than 390 or 240 ms, respectively, to be at risk for recurrence of symptoms. A patient likely to have recurrence of symptoms would have values located in the lower left corner of Figure 5: repetitive ventricular response status changing from negative to positive and ventricular tachycardia easier to induce; this patient has a high probability of having recurrent ventricular tachycardia regardless of the change in QT_c interval or ventricular effective refractory period.

Discussion

Discriminant analysis. The most important new observation in this study is that use of multiple variables obtained during serial electrophysiologic testing can accurately classify clinical outcome in patients receiving amiodarone in whom ventricular tachycardia is induced during programmed ventricular stimulation. Previous investigations (13–15) suggested that whereas noninduction of ventricular tachycardia during programmed ventricular stimulation predicts a favorable clinical outcome, induction of ventricular tachycardia does not yield accurate predictive data regarding clinical efficacy of amiodarone treatment (3–5,7). However, the latter studies used only induction of ventricular tachycardia as an end point to predict patients likely to have recurrent arrhythmias, on the basis of earlier investigations showing that failure to prevent ventricular tachycardia initiation during conventional drug therapy augured a high probability of spontaneous recurrence of ventricular tachycardia or sudden death (16,17). This latter approach does not appear to be useful for amiodarone therapy.

Change in repetitive ventricular response status. The variables used in the discriminant analysis were change in repetitive ventricular response status, change in mode of

Table 6. Discriminant Analysis (RVR, Δ VERP and Δ induction method)

Actual Group (n = 25)	Assigned Group: Asymptomatic	Assigned Group: Symptomatic
Asymptomatic 18	16	2
Symptomatic 7	0	7
Classification accuracy = 92.0% (23 of 25)		

Risk Factors	Structure Coefficient	p Value
Δ VERP	0.16	<0.001
RVR	0.58	0.005
Δ Ind method	0.42	<0.001
RVR − to + = +1	Ind easier = +1	
RVR same = 0	Ind same = 0	
RVR + to − = −1	Ind harder = −1	

Critical value = 0.523. Discriminant function = −0.645 + 2.182 (RVR) + 1.449 (Ind) − 0.020 (Δ VERP). Δ VERP = ventricular effective refractory period (drug) − ventricular effective refractory period (control); other abbreviations as in previous tables.

METHOD OF VT INDUCTION	CHANGE IN RVR STATUS: Neg to Pos	Pos to Neg	Same
Harder	▲ QTc > 26 ms ▲ VERP > 22 ms	▲ QTc > 390 ms ▲ VERP > 240 ms	▲ QTc > 213 ms ▲ VERP > 131 ms
Same	▲ QTc ≥ 0 ▲ VERP ≥ 0	▲ QTc > 287 ms ▲ VERP > 167 ms	▲ QTc > 110 ms ▲ VERP > 58 ms
Easier	▲ QTc ≥ 0 ▲ VERP ≥ 0	▲ QTc > 184 ms ▲ VERP > 95 ms	▲ QTc ≥ 0 ▲ VERP ≥ 0

Figure 5. Risk of recurrent events for patients who have ventricular tachycardia (VT) induced during amiodarone therapy. Ventricular tachycardia is more likely to recur if the constellation of conditions in any one of the boxes is met. It is less likely to recur if they are not met. Either Δ QT_c or Δ VERP may be utilized. Predictive accuracy is greater than 90% in our patients. Δ QT_c = QT_c (control study) − QT_c (drug study); Δ VERP = ventricular effective refractory period (VERP) (control study) − VERP (drug study). Change in repetitive ventricular response (RVR) status and comparison of ventricular tachycardia induction method are in the direction of control to drug study.

ventricular tachycardia induction and change in either QT interval or ventricular effective refractory period. The induction of repetitive ventricular responses by ventricular extrastimuli introduced during sinus rhythm is not sensitive enough to be clinically useful by itself (8). This was also true in the present study, but we found that data on repetitive ventricular response status were useful if combined with other variables, as suggested previously (8). Thus, in patients who have ventricular tachycardia initiated during amiodarone therapy, a change in repetitive ventricular response induction from positive to negative suggests a favorable outcome, but a change from negative to positive suggests an unfavorable outcome (Fig. 5).

Change in mode of induction. The second major variable in the discriminant function equation is change in pacing technique used to initiate ventricular tachycardia. The hierarchy of aggressiveness of pacing mode to induce ventricular tachycardia (Fig. 1) is arbitrary, as judged by our experience and the results of other investigators (18,19). Commonly, two extrastimuli delivered during ventricular pacing ($V_1V_2V_3$) are necessary to initiate ventricular tachycardia at control study (19), and this technique was necessary to induce ventricular tachycardia in 25 of the 37 patients. Ventricular extrastimuli introduced during sinus rhythm (RV_2, RV_2V_3) do not commonly induce ventricular tachycardia, and only 2 of 37 patients had ventricular tachycardia initiated with this pacing mode before drug therapy. During amiodarone therapy the RV_2 or RV_2V_3 pacing technique induced ventricular tachycardia in 6 of 14 symptomatic patients but in only 1 of 23 asymptomatic patients (Fig. 3). Because most of the former patients also changed from a negative to a positive repetitive ventricular response, they represent a classification with a high probability of recurrence of symptoms (Fig. 5).

One potential problem with the hierarchy of pacing techniques is presenting burst pacing as the most aggressive technique. Because we now believe that burst pacing has poor reproducibility, we use instead three extrastimuli if ventricular tachycardia is not initiated by one or two extrastimuli. However, burst pacing added little to the data in this study, because only one patient required this technique to initiate ventricular tachycardia before drug therapy (Fig. 3).

Spontaneous arrhythmia suppression. We evaluated whether premature ventricular complex suppression alone or in combination with other variables was useful to predict drug success or failure. Our data differ from those of Nademanee et al. (7), who evaluated premature ventricular complex suppression between 2 and 8 weeks of amiodarone therapy. We were unable to demonstrate usefulness of premature ventricular complex suppression after 2 weeks of therapy as a univariate or multivariate variable to classify patients likely to be symptomatic or asymptomatic. In fact, amiodarone caused a greater than 90% decrease in premature ventricular complex counts per 24 hours in equal numbers of symptomatic and asymptomatic patients. It should be noted that these conclusions are made on the basis of a relatively small sample size, and sampling of a larger patient population may yield different results.

Timing of electrophysiologic testing during amiodarone therapy. The half-life of amiodarone is approximately 1 month (20), and it could be argued that electrophysiologic testing should have been performed after more than 14 days of amiodarone treatment. However, Finerman et al. (21) studied patients after a mean of 11 weeks of amiodarone therapy and demonstrated electrophysiologic changes similar to those we noted (3). Furthermore, recent data from Ferrick et al. (22) show that ventricular tachycardia induced after 2 weeks of amiodarone therapy in almost all patients can still be induced after 3 months of therapy. It is unreasonable to keep patients hospitalized for months before restudy at steady state amiodarone conditions, yet many patients will have recurrent arrhythmias or sudden death after hospital discharge, as noted in 14 (38%) of our 37 patients (Fig. 2). Thus, we believe it is important to develop methods to correctly classify those patients with inducible ventricular tachycardia during amiodarone therapy before hospital discharge who are likely to have ventricular tachycardia or cardiac arrest after hospital discharge. In the present study we used discriminant analysis with multiple variables to predict clinical outcome and to arrive at this decision early in the patient's course of therapy.

Our present approach to patients who have ventricular tachycardia induced during amiodarone therapy and appear to be at increased risk for recurrence of ventricular arrhythmias during follow-up is to modify their drug therapy or

choose alternative forms of therapy, such as surgery. Further investigations at other medical centers are needed to determine whether the proposed discriminant function can be used to predict clinical outcome of patients treated with amiodarone.

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